This listing of claims will replace all prior versions, and listings, of claims in the application (material to be inserted is in **bold and underline**, material to be deleted is in ~~strikeout~~):

**Listing of Claims:**

1. (Currently Amended) A pair of oligonucleotide primers for use in detecting the presence or absence of an enterovirus in a sample, wherein a first primer of said pair ~~comprises~~ **consists of** a sequence of any of:

SEQ ID NO: 1: TTGTRCGCCTGTTTTA,

SEQ ID NO: 2: CAAGCACTTCTGTHHCCCCGG,

SEQ ID NO: 3: TACTTCGAGAARCCYAGTA,

SEQ ID NO: 4: AAGAGYCTATTGAGCTA, or

SEQ ID NO: 5: GGITGGTRSTGGAARTTICC, or a degenerate sequence of SEQ ID No: 5; and

a second primer of said pair ~~comprises~~ **consists of** a sequence of any of:

SEQ ID NO: 6: CACYGGATGGCCAATCCAA,

SEQ ID NO: 7: ATTGTCACCATAAGCAGCCA, or

SEQ ID NO: 8: ARRTTIATCCAYTGRTGIGG, or a degenerate sequence of SEQ ID No: 8, where the first primer and the second primer can be employed to amplify a sequence of a conserved portion in the nucleic acids of enteroviruses,

provided that the second primer ~~comprises~~ **consists of** the sequence of SEQ ID NO: 8

or a degenerate sequence of SEQ ID NO: 8 when the first primer ~~comprises~~ **consists of** the sequence of SEQ ID NO: 5 or a degenerate sequence of SEQ ID NO: 5.

2. (Currently Amended) A pair of primers according to claim 1, ~~which comprises a sequence~~ selected from the group consisting of: SEQ ID NO: 1/SEQ ID NO: 6; SEQ ID NO: 2/SEQ ID NO: 6; SEQ ID NO: 3/SEQ ID NO: 6; SEQ ID NO: 4/SEQ ID NO: 6; SEQ ID NO: 1/SEQ ID NO: 7; SEQ ID NO: 2/SEQ ID NO: 7; SEQ ID NO: 3/SEQ ID NO: 7; SEQ ID NO: 4/SEQ ID NO: 7; and SEQ ID NO: 5/SEQ ID NO: 8.

3. (Original) A pair of primers according to claim 1, which is SEQ ID NO: 5/SEQ ID NO: 8.

4. (Original) A pair of primers according to claim 3 for use in the detection of enterovirus type 71 (EV71) or coxasackievirus A16 (Cox A 16).

5. (Currently Amended) A synthetic nucleotide ~~comprising~~ **consisting of** a conserved portion in the nucleic acids of enteroviruses, said sequence being selected from the group consisting of:

SEQ ID NO: 9: TCCTCCGGCCCCTGAATGCGGCTAATC,

SEQ ID NO: 10: TGTCGTAACGSGCAASTCYGYRGCGGAACCGAC,

SEQ ID NO: 11: TACTTTGGGTGTCCGTGTTTCHTTTTAT,

SEQ ID NO: 12: CTTATAAGCAGACTCAACCCGGTGCTGATG,

SEQ ID NO: 13: TGGCATTCCAATATCACAATTAACAGTG,

SEQ ID NO: 14: CTCGGCACTATCGCAGGAGGGACCGGGAAT and

SEQ ID NO: 15: CCTACGCCACTACACAGCCTGGTCAGGTTG, and a degenerate sequence of any of SEQ ID Nos.: 12 15,

Which specifically hybridizes to a sense strand of an enterovirus nucleic acid or a nucleic acid comprising the sense strand.

6 - 20. Withdrawn from consideration.

21. (Currently Amended) A kit for detecting an enterovirus in a sample, which comprises at least one pair of oligonucleotide primers according to claim 1, provided that the second primer ~~comprises~~ **consists of** the sequence of SEQ ID NO: 8 or a degenerate sequence thereof when the first primer ~~comprises~~ **consists of** the sequence of SEQ ID NO: 5 or a degenerate sequence thereof.

22. (Original) A kit according to claim 21, which comprises more than one pair of oligonucleotide primers according to claim 1.

23. (Currently Amended) A kit according to claim 22, which further comprises at least one synthetic nucleotide sequence according to claim 5,

~~provided that the nucleotide sequence does not comprise a sequence of any of SEQ ID Nos:12-15 nor a degenerate sequence thereof when the second primer comprising the sequence of SEQ~~

~~ID NO:8 or a degenerate sequence thereof is not employed for amplification, and that the nucleotide sequence does not comprise a sequence of any of SEQ ID Nos:9-11 when the first primer comprising the sequence of SEQ ID NO:5 or a degenerate sequence thereof is not employed for amplification~~

**provided that where the second primer consists of one of SEQ ID Nos.: 6-7 the nucleotide sequence consists of one of SEQ ID Nos.: 9-11; and that where the first primer consists of one of SEQ ID Nos.: 1-4, the nucleotide sequence consists of one of SEQ ID Nos.: 12-15 and a degenerate sequence of any of SEQ ID Nos.: 12 and 15**.

24. (Currently Amended) A kit for detecting and differentiating enterovirus type 71 in a sample, which comprises

at least one pair of oligonucleotide primers according to claim 1, provided that the second primer ~~comprises~~ **consists of** the sequence of SEQ ID NO:8 or a degenerate sequence thereof; and

at least one synthetic nucleotide sequence ~~comprising~~ **consisting of** the sequence of SEQ ID NO:12 or SEQ ID NO:13.

25. (Currently Amended) A kit for detecting and differentiating coxsackievirus A16 in a sample, which comprises:

at least one pair of oligonucleotide primers according to claim 1, provided that the second primer ~~comprises~~ **consists of** the sequence of SEQ ID NO:8 or a degenerate sequence thereof; and

at least one synthetic nucleotide sequence ~~comprising~~ **consisting of** the sequence of SEQ ID NO:14 or SEQ ID NO:15.

26. (Currently Amended) A kit for detecting and differentiating enterovirus type 71 and/or coxsackievirus A16 in a sample, which comprises:

at least one pair of oligonucleotide primers according to claim 1, provided that the second primer ~~comprises~~ **consists of** the sequence of SEQ ID NO:8 or a degenerate sequence thereof; and

at least a first synthetic nucleotide sequence ~~comprising~~ **consisting of** the sequence of SEQ ID NO:12 or SEQ ID NO:13 and at least a second synthetic nucleotide sequence ~~comprising~~ **consisting of** the sequence of SEQ ID NO:14 or SEQ ID NO:15.

27. (New) A kit for detecting and differentiating an enterovirus in a sample, comprising at least one pair of oligonucleotide primers for nucleic acid amplification, wherein a first primer of said pair consists of a sequence of any of:

SEQ ID NO: 1: TTGTRCGCCTGTTTTA,

SEQ ID NO: 2: CAAGCACTTCTGTHHCCCCGG,

SEQ ID NO: 3: TACTTCGAGAARCCYAGTA,

SEQ ID NO: 4: AAGAGYCTATTGAGCTA, or

SEQ ID NO: 5: GGITGGTRSTGGAARTTICC, or a degenerate sequence of SEQ ID No: 5; and

a second primer of said pair consists of a sequence of any of:

SEQ ID NO: 6: CACYGGATGGCCAATCCAA,

SEQ ID NO: 7: ATTGTCACCATAAGCAGCCA, or

SEQ ID NO: 8: ARRTTIATCCAYTGRTGIGG, or a degenerate sequence of SEQ ID No: 8, provided that the second primer consists of the sequence of SEQ ID NO: 8 or a degenerate sequence thereof when the first primer consists of the sequence of SEQ ID NO: 5 or a degenerate sequence of SEQ ID NO: 5; and

at least one synthetic nucleotide seque3nce fixed on a solid substrate for nucleic acid hybridization with nucleic acids obtained from the amplification, wherein the synthetic nucleotide comprises any sequence selected from the group consisting of:

SEQ ID NO: 9: TCCTCCGGCCCCTGAATGCGGCTAATC,

SEQ ID NO: 10: TGTCGTAACGSGCAASTCYGYRGCGGAACCGAC,

SEQ ID NO: 11: TACTTTGGGTGTCCGTGTTTCHTTTTAT,

SEQ ID NO: 12: CTTATAAGCAGACTCAACCCGGTGCTGATG,

SEQ ID NO: 13: TGGCATTCCAATATCACAATTAACAGTG,

SEQ ID NO: 14: CTCGGCACTATCGCAGGAGGGACCGGGAAT and

SEQ ID NO: 15: CCTACGCCACTACACAGCCTGGTCAGGTTG, and a degenerate sequence of any of SEQ ID Nos.: 12 15.

28. (New) A kit for detecting and differentiating an enterovirus in a sample, comprising at least one synthetic nucleotide sequence fixed on a solid substrate for nucleic acid hybridization with nucleic acids in the sample, wherein the synthetic nucleotide sequences consists of any sequence selected from the group consisting of

SEQ ID NO: 9: TCCTCCGGCCCCTGAATGCGGCTAATC,

SEQ ID NO: 10: TGTCGTAACGSGCAASTCYGYRGCGGAACCGAC,

SEQ ID NO: 11: TACTTTGGGTGTCCGTGTTTCHTTTTAT,

SEQ ID NO: 12: CTTATAAGCAGACTCAACCCGGTGCTGATG,

SEQ ID NO: 13: TGGCATTCCAATATCACAATTAACAGTG,

SEQ ID NO: 14: CTCGGCACTATCGCAGGAGGGACCGGGAAT and

SEQ ID NO: 15: CCTACGCCACTACACAGCCTGGTCAGGTTG, and a degenerate sequence of any of SEQ ID Nos.: 12 15.

## REMARKS

Claims 1-26 are pending in the application. Claims 6-20 are withdrawn from consideration. Claims 1-5 and 21-26 are rejected. Claims 1, 2, 5, 21, and 23-26 are amended. New claims 27 and 28 are added. In view of the above amendments and the remarks below, applicants request reconsideration of the claims.

Applicants thank the examiner for the courtesy of a telephonic interview on July 31, 2003.

***Rejections under 35 U.S.C. § 112***

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

Applicant has amended claim 23 to more particularly define the claimed invention. As amended, applicants suggest that claim 23, as amended, further limits the subject matter of claim 22, and further that specific combinations of primers are permitted that allow nucleotide sequences according to claim 5 to be present. In view of the above amendments, applicants request the withdrawal of the rejection of claim 23 under 35 U.S.C. § 112.

***Rejections under 35 U.S.C. § 102***

Claim 5 is rejection under 35 U.S.C. § 102(a) as being anticipated by Accession number AF136379 (June 2000). Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number Z78129 (August 1997). Claim 5 is rejected under 35 U.S.C. § 102(b) as being anticipated by Accession number U55870 (May 1996). The action indicates that the cited references disclose sequences that include the indicated SEQ ID Nos. of claim 5,

and therefore meet the limitation of "a nucleotide comprising a conserved portion in the nucleic acids of enteroviruses" as the recitation of 'comprising' encompasses sequences on either side of the conserved portions.

Applicants have amended claim 5 to replace the "comprising" language of the claims with "consisting of" language, and suggest that the cited references fail to disclose the discrete conserved portions of the enterovirus nucleotide sequences set out in the claims. In view of the above amendment, the applicants request the withdrawal of the rejection of claim 5 under 35 U.S.C. § 102.

***Rejections under 35 U.S.C. § 103***

Claims 1-5 and 21-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kilpatrick (U.S. Patent No. 6,168,917) in view of Accession numbers U22521 (January 1997), AF 177911 (September 1999), AF136379 (June 2000), U55870 (May 1996) and Z78129 (August 1997) and further in view of Accession number E30248 (from JP 1999346799).

Applicants have amended claims 1, 2, 5, 21, and 23-26 to replace the "comprising" language of the claims with "consisting of" language, and suggest that the cited references fail to suggest that the discrete conserved portions of the enterovirus nucleotide sequences set out in the claims, and fail to suggest the advantageous utility of such conserved regions for simultaneous detection and differentiation of enterovirus, as set out in the claims.

The action indicates that "although Kilpatrick in view of the recited accession numbers *do not teach* the specific primer pair and nucleotide sequences of the claimed invention, armed with the teachings of Kilpatrick, the ordinary artisan *would have been able to* develop primer

pairs and nucleotide sequences that would specifically detect Enterovirus 72 and Coxsackievirus A16" (emphasis added). However, as set out at MPEP § 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.

The action further indicates that "given that the sequences of the genome of many enteroviruses were already sequenced and readily available, *it would have been well within the skill of the ordinary artisan* to align these known sequences and identify conserved and variable regions" (emphasis added). However, also as set forth at MPEP § 2143.01, the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish prima facie obviousness, without some objective motivation to combine the teachings of the references. That motivation cannot be found in the applicants' own specification.

Even the fact that there was a need for efficient and sensitive assays for enteroviruses does not provide sufficient motivation for the selection of the particular conserved regions set out in the instant claims. At most, such a need might provide a motivation to engage in experimentation in order to formulate such an assay. However, "obvious to try" is not the standard for establishing *prima facie* obviousness under 35 U.S.C. 103, rather a reasonable expectation of success of the claimed invention is required, and that reasonable expectation must be found in the cited references themselves (see MPEP 2143.02).

Applicants suggest an improper standard of *prima facie* obviousness has been applied. The action has failed to identify specific motivation in the cited references to modify the references so as to arrive at the claimed invention. The action has failed to provide a

reasonable expectation of success of the claimed invention. Applicants therefore suggest that the action has failed to establish the obviousness of the rejected claims, and they request the withdrawal of the rejection of claims 1-5 and 21-26 under 35 U.S.C. § 103.

Applicants take this opportunity to add new claims 27 and 28, which are drawn to selected kits useful for the detection and differentiation of enterovirus in a sample. Claims 27 and 28 are intended to further the prosecution of the application by providing particularly defined and allowable subject matter. The kits of claims 27 and 28 include at least one synthetic nucleotide sequence fixed on a solid substrate for nucleic acid hybridization with nucleic acids in the sample, providing for facile and efficient detection of hybridization signals by the user of the claimed kits. Support for claims 27 and 28 may be generally found in claims 1-25 as originally filed, and in the specification at page 14, lines 14-24. Applicants suggest that the kits of claims 27 and 28 are novel and unobvious over the cited prior art, and are therefore in condition for allowance.

***Rejoinder of withdrawn claims***

Applicants suggest that the claims as amended are in condition for allowance. It is therefore requested that previously withdrawn claims 6-20 be rejoined in the application, as withdrawn process claims which depend from or otherwise include all the limitations of an allowable product claim will be rejoined (see MPEP § 821.04).

The above amendments and remarks are believed to address fully the Examiner's rejections, and place the application in condition for allowance. A prompt indication of the same respectfully is requested. The Examiner is encouraged to telephone the undersigned if any issues remain that may be resolved by a telephonic interview.

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on August 19, 2003.

George Painter

George Painter
Date of Signature: August 19, 2003

Respectfully submitted,
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